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Glycemic control and hypoglycemia benefits with insulin glargine 300 U/mL (Gla-300) extend to people with type 2 diabetes and mild-to-moderate renal impairment

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Abstract

Aims:

Impaired renal function increases hypoglycemia risk in type 2 diabetes (T2DM). Insulin glargine 300 U/mL (Gla-300) has previously demonstrated reduced hypoglycemia risk versus insulin glargine 100 U/mL (Gla-100). Therefore, we investigated the impact of renal function on the safety and efficacy of Gla-300 and Gla-100.

Materials and Methods:

A meta-analysis was performed using pooled 6-month data from the EDITION 1, 2 and 3 trials (N=2496). Eligible participants, aged ≥18 years with a diagnosis of T2DM, were randomized to receive once-daily evening injections of Gla-300 or Gla-100. Pooled results were assessed by two renal function subgroups: estimated glomerular filtration rate (eGFR) <60 and ≥60 mL/min/1.73 m^2.

Results:

The decrease in HbA_{1c} after 6 months and the proportion of individuals with T2DM achieving HbA_{1c} targets were comparable between Gla-300 and Gla-100, for both renal function subgroups. There was a reduced risk of nocturnal (00:00–05:59 h) confirmed (≤70 mg/dL [≤3.9 mmol/L]) or severe hypoglycemia with Gla-300 in both renal function subgroups (eGFR <60 relative risk [RR] 0.76 [95% CI 0.62–0.94] and ≥60 0.75 [0.67–0.85]). For confirmed (≤70 mg/dL [≤3.9 mmol/L]) or severe hypoglycemia at any time of day (24 h) the hypoglycemia risk was lower with Gla-

300 versus Gla-100 in both the lower (RR 0.94 [0.86–1.03]) and higher (RR 0.90 0.85–0.95]) eGFR subgroups.

Conclusions:

Gla-300 provided comparable glycemic control to Gla-100, while indicating a reduced overall risk of confirmed (≤70 and <54 mg/dL [≤3.9 and <3.0 mmol/L]) or severe hypoglycemia with no significant difference between renal function subgroups.

Introduction

Diabetes and chronic kidney disease (CKD) are common chronic comorbid conditions, with diabetic kidney disease accounting for approximately half of all end-stage renal disease cases in developed countries.[1] The US National Health and Nutrition Examination Survey (NHANES) reported that approximately 40% of survey participants with diabetes had CKD.[2] Similarly, in the UK, CKD stage 3 was reported in approximately 29% of individuals with diabetes, versus approximately 7% of those without diabetes[3], while CKD stage 4 and 5 was reported in 2.1% versus 0.2%, and 0.3% versus 0.03% of individuals with and without diabetes, respectively.[3] Additionally, the incidence of CKD in diabetes may be under-reported, with one US primary care study indicating that CKD stages 1–5 affected 54% of individuals with type 2 diabetes (T2DM), although it had only been diagnosed in 12% of cases.[4] Rates of CKD are higher in elderly populations, and as the proportion of people aged over 60 years increases so will the rates of CKD.[5]

Renal impairment complicates the management of diabetes because it increases the risk of hypoglycemia, is associated with increased risk of cardiovascular morbidity and mortality, and limits the options for glucose-lowering therapy.[6-9] For example, cardiovascular disease has been reported in 53% of people with CKD,[10] and as high as 59% of people who also have T2DM.[4] The rate of hypoglycemia in people with diabetes and CKD can be double that of individuals without CKD,[11] therefore the choice of glucose-lowering therapy should account for this increased risk.[6, 8] Additionally, dose adjustments, or even drug withdrawal, may be necessary, as the

clearance of some therapies may be affected.[8] However, there is a lack of evidence available, particularly from randomized clinical trials, to inform the choice of therapy and treatment goals in the management of diabetes in people with renal impairment,[8] or regarding optimal glycemic control in individuals with diabetes and more advanced CKD, for whom HbA_{1c} targets >7.0 % may be appropriate.[8]

For people with T2DM and CKD, insulin remains an appropriate option when other agents such as metformin may be contraindicated or are used at lower than standard doses.[12] While insulin requirements are generally lower in people with impaired renal function, there are no specific guidelines regarding insulin dose adjustment in this population other than general recommendations that glycemic targets should be individualized.[8] Insulin glargine 300 U/mL (Gla-300), a second-generation basal insulin, provides a more stable and prolonged pharmacokinetic and pharmacodynamic (PK/PD) profile compared with insulin glargine 100 U/mL (Gla-100).[13] Data from the phase 3 EDITION 1, 2 and 3 clinical trials showed that over 6 months, Gla-300 provided comparable glycemic control to Gla-100 in participants with T2DM, with less hypoglycemia.[14-16] Given the reduced hypoglycemia risk with Gla-300 versus Gla-100, we were interested to see if this benefit persisted in individuals with impaired renal function. The objective of this post hoc patient-level meta-analysis of EDITION 1, 2 and 3 was to investigate the impact of renal function on the safety and efficacy of Gla-300, with a focus on hypoglycemia risk.

Materials and Methods

Study design and participants

EDITION 1, 2 and 3 (NCT01499082, NCT01499095, NCT01676220) were multicenter, randomized (1:1), open-label, two-arm, parallel-group, phase 3a studies.[14-16] Briefly, eligible participants were aged ≥18 years with T2DM and receiving the following: EDITION 1, basal (≥42 U/day) and prandial insulin therapy ± metformin for ≥1 year; EDITION 2, basal insulin therapy (≥42 U/day) in combination with OADs; EDITION 3, OADs received for ≥6 months before screening and insulin-naïve. People with severe, unstable or end-stage renal disease (CKD stage 5, estimated glomerular filtration rate [eGFR] <15 mL/min/1.73 m^2) were excluded. Participants were randomized (1:1) to once-daily evening injections of Gla-300 (Toujeo®, Sanofi, Paris, France) or Gla-100 (Lantus®, Sanofi), titrated to a fasting self-monitored plasma glucose (SMPG) target of 80–100 mg/dL (4.4–5.6 mmol/L); sulfonylurea use was not allowed.

In this post hoc analysis, study populations were pooled and results assessed across two renal function subgroups, according to baseline eGFR (calculated using the Modification of Diet in Renal Disease [MDRD] study equation): ≥15 to <60 (CKD stage 3–4, indicating mild-to-moderate renal impairment) and ≥60 mL/min/1.73 m^2 (indicating preserved renal function).

Outcomes

The following endpoints were examined: HbA_{1c} and fasting plasma glucose (FPG) change from baseline to month 6, percentage of participants achieving HbA_{1c} <7.0 % and <7.5 % at month 6, percentage of participants attaining FPG <5.6 mmol/L and <6.7 mmol/L, change in insulin dose and body weight from baseline to month 6, percentage of participants with ≥1 hypoglycemic event, hypoglycemic event rates per participant-year and cumulative mean number of hypoglycemic events per participant (during the night [00:00–05:59 h] or at any time of day [24 h]), and adverse events during the 6-month study period. Hypoglycemia endpoints were based on American Diabetes Association (ADA) definitions [17]; confirmed or severe hypoglycemia was defined as any event that was documented symptomatic or asymptomatic with a plasma glucose measurement of ≤70 mg/dL or <54 mg/dL, or severe (requiring third-party assistance).

Data analysis and statistics

Efficacy outcomes were analyzed using the modified intent-to-treat (mITT) population, defined as all randomized participants who received at least one dose of study insulin and had both a baseline and at least one post-baseline efficacy assessment. The safety population comprised all participants who had received at least one dose of study insulin.

Change in HbA_{1c} was analyzed using a mixed model for repeated measurements (MMRM) approach. Relative risk of hypoglycemia was analyzed using the Cochran-Mantel-Haenzel (CMH) method and annualized rates of hypoglycemia were analyzed using an overdispersed Poisson regression model. For HbA_{1c}, and hypoglycemia, the homogeneity of the treatment effect among subgroups was assessed using subgroup-by-treatment interaction. Differences of treatment effect across subgroups were only considered relevant if significant heterogeneity was observed ($p<0.05$). Body weight, insulin dose, FPG, AEs and patient satisfaction (evaluated using the Diabetes Treatment Satisfaction Questionnaire [DTSQ]) were assessed descriptively.

Results

Baseline characteristics

The mITT and safety populations included 2474 and 2488 individuals, respectively. Of the 2496 participants randomized to treatment in EDITION 1, 2 and 3, 2075 (83.1%) had a baseline eGFR ≥60 mL/min/1.73 m^2 (Gla-300: n=1039; Gla-100: 1036) and 421 (16.9%) had a baseline eGFR <60 mL/min/1.73 m^2 (Gla-300: n=208; Gla-100: 213). Baseline characteristics are summarized in **Table 1**. Participants were, on average, older in the lower versus higher eGFR subgroup (approximately 65 years versus 57 years). Most participants in the study were Caucasian. Mean duration of diabetes was longer in the lower versus higher eGFR subgroup (approximately 16 years versus 12 years). Those in the lower eGFR subgroup had

received approximately 1 year more of insulin therapy than those in the higher eGFR subgroup.

The proportions of participants with comorbidities reported at baseline were similar between renal function subgroups (Supplementary Table 1), although there was a general trend for more participants reporting complications in the lower eGFR subgroup. The most common overall complication was diabetic sensory and motor neuropathy, reported in approximately 41% and 32% of participants in the lower and higher eGFR subgroups, respectively. Diabetic macroangiopathy was reported in an average of 9.1% and 6.1% of participants in the lower and higher eGFR subgroups, respectively (Supplementary Table 1). Cardiac disorders were documented in 39.2% of participants in the lower eGFR subgroup, compared with 25.4% in the higher eGFR subgroup.

Renal function

The EDITION 1 study contributed the largest proportion of participants to the <60 mL/min/1.73 m^2 subgroup (n=188) (Supplementary Table 2). At baseline, the pooled average eGFR for the lower and higher renal function subgroups were 48.6 mL/min/1.73 m^2 and 85.0 mL/min/1.73 m^2, respectively. These values did not change markedly after 6 months' treatment, regardless of eGFR subgroup or treatment arm (50.5 mL/min/1.73 m^2 and 85.0 mL/min/1.73 m^2).

Previous and concomitant medications

At baseline, most participants were using non-insulin antihyperglycemic medications (approximately 75% and 88% in the lower and higher eGFR subgroups, respectively), of which metformin was the most common (Table 1). The proportion of participants using metformin in the lower eGFR subgroup (55%) was less than in the higher eGFR subgroup (68%). By comparison, more participants in the lower eGFR subgroup than in the higher eGFR subgroup had previously been using insulins (72% and 63%, respectively) or antihypertensive agents (86% and 74%, respectively). Most participants were using statins, irrespective of renal function (Table 1). At month 6, there was very little change in medication usage patterns from baseline in either treatment arm or renal function subgroup (Supplementary Table 3).

Glycemic control

HbA_{1c} reduction from baseline was comparable between the Gla-300 and Gla-100 treatment groups, regardless of renal function (Least Squares [LS] mean difference 0.14 [95% confidence interval (CI): –0.04 to 0.32 and –0.03 [95% CI: –0.11 to 0.05]) in the eGFR <60 and ≥60 subgroups, respectively. There was no evidence of heterogeneity of treatment effect across subgroups (p=0.097; Figure 1A). Similar proportions of participants achieved HbA_{1c} target <7.0 % between treatment arms in both renal function subgroups. In the lower eGFR subgroup, 36.4% and 39.2% of participants achieved target with Gla-300 and Gla-100, respectively. In the higher eGFR subgroup, 36.2% and 34.7% of participants achieved target with Gla-300 and Gla-100 (Figure 1B). As observed for the HbA_{1c} <7.0 % target, the proportion of

participants achieving HbA_{1c} target <7.5 % was comparable between the Gla-300 and Gla-100 treatment arms in both renal function subgroups. In the Gla-300 and Gla-100 treatment arms respectively, 54.9% and 58.4% of participants achieved target in the lower eGFR subgroup, and 54.0% and 51.8% of participants achieved target in the higher eGFR subgroup. The mean change in FPG from baseline to month 6 was comparable for both treatment arms and renal function subgroups (Supplementary Table 4). The proportion of participants attaining FPG <5.6 mmol/L was 24.8% and 32.5% in the lower eGFR subgroup, and 25.2% and 25.1% in the higher eGFR subgroup, with Gla-300 and Gla-100, respectively; for attainment of FPG <6.7 mmol/L, the proportions were 45.1% and 50.2% in the lower eGFR subgroup, and 44.5% and 46.6% in the higher eGFR subgroup, with Gla-300 and Gla-100, respectively.

Hypoglycemia

More participants in the lower versus the higher eGFR subgroup experienced ≥1 confirmed (≤70 mg/dL [≤3.9 mmol/L] and <54 mg/dL [<3.0 mmol/L]) or severe hypoglycemic event at night (00:00–05:59 h) or at any time of day (24 h), regardless of the insulin used (Figure 2A). The relative risk of confirmed (≤70 mg/dL [≤3.9 mmol/L]) or severe hypoglycemic events at night (00:00–05:59 h) was lower with Gla-300 than with Gla-100 RR 0.76 [95% CI: 0.62 to 0.94] and 0.75 [95% CI: 0.67 to 0.85] in the lower and higher eGFR subgroups, respectively. Similarly, the risk of any time of day (24 h) confirmed (≤70 mg/dL [≤3.9 mmol/L]) or severe hypoglycemic events was lower with Gla-300 than with Gla-100 in the lower and higher eGFR

subgroups (RR 0.94 [95% CI 0.86 to 1.03 and 0.90 [95% CI 0.85 to 0.95], respectively). There was no significant difference between renal function subgroups (no evidence of heterogeneity of treatment effect across subgroups, p=0.662 for nocturnal events; p=0.794 for events at any time of day). Consistent results were observed when using the more stringent glycemic threshold of <54 mg/dL (<3.0 mmol/L) (Figure 2B).

The rates of confirmed or severe nocturnal (00:00–05:59 h) or any time (24 h) hypoglycemia events per participant-year, at both glycemic thresholds, were higher in the lower versus the higher eGFR subgroup, irrespective of the insulin used (Figure 3A). The annualized rate of confirmed (≤70 mg/dL [≤3.9 mmol/L]) or severe hypoglycemic events at night (00:00–05:59 h) and at any time of day (24 h) in the overall population was lower with Gla-300 than with Gla-100 (Figure 3B), and there was no significant difference between renal function subgroups (no evidence of heterogeneity of treatment effect across subgroups, p=0.986 for nocturnal events; p=0.604 for events at any time of day). The rate ratio of nocturnal confirmed (≤70 mg/dL [≤3.9 mmol/L]) or severe hypoglycemic event was 0.69 [95% CI: 0.44 to 1.08] in the lower and 0.69 [95% CI: 0.56–0.85] in the higher eGFR subgroup. Similarly, for any time of day (24 h) confirmed (≤70 mg/dL [≤3.9 mmol/L]) or severe hypoglycemia the rate ratios for Gla-300 versus Gla-100 were 0.81 [95% CI:0.64 to 1.04] in the lower eGFR subgroup and 0.88 [95% CI: 0.77 to 1.00] in the higher eGFR subgroup. Generally, these results were consistent at the lower glucose threshold, with an overall lower annualized rate of nocturnal events for Gla-300 versus Gla-100, but not for hypoglycemic events that occurred at any time of day

(Figure 3B), and no heterogeneity of treatment effect across the subgroups (p=0.707 for nocturnal events; p=0.792 for events at any time of day).

Severe hypoglycemia was experienced by 28/1242 (2.3%) participants in the Gla-300 group (lower eGFR subgroup: 11/207 [5.3%]; higher eGFR subgroup: 17/1035 [1.6%]) and 33/1236 (2.6%) in the Gla-100 group (lower eGFR subgroup: 9/212 [4.2%]; higher eGFR subgroup: 24/1034 [2.3%]). Annualized rates of severe hypoglycemic events at any time of day (24 h) were 0.35 and 0.26 events per participant-year in the Gla-300 and Gla-100 treatment groups, respectively, for participants in the lower eGFR subgroup. For the higher eGFR subgroup, annualized rates were 0.06 and 0.08 events per participant-year, respectively.

The proportion of participants who achieved HbA_{1c} targets (<7.0 % or <7.5 %) without experiencing confirmed or severe hypoglycemia were comparable across renal function subgroups and between treatment arms, for both hypoglycemia thresholds evaluated (Supplementary Table 5).

Body weight and insulin dose

Mean (SD) change in body weight from baseline to month 6 was small in both treatment groups across both renal function subgroups: 0.14 (4.06) kg and 0.42 (3.68) kg for participants in the lower eGFR subgroup; 0.59 (3.48) kg and 0.92 (3.20)

kg for participants in the higher eGFR subgroup, in the Gla-300 and Gla-100 groups, respectively. At month 6, insulin dose in the lower eGFR subgroup increased from baseline by 0.30 and 0.21 U/kg (an average increase of 89.3% and 72.4%) for Gla-300 and Gla-100, respectively. In the higher eGFR subgroup, the insulin dose increase from baseline was 0.35 and 0.26 U/kg (an average increase of 117.0% and 89.2%) for Gla-300 and Gla-100, respectively (Supplementary Table 4). This reflected a −23.7% difference in dose increase for Gla-300 and a −18.8% difference in dose increase for Gla-100 between the lower versus higher eGFR subgroups.

Adverse events

Treatment-emergent adverse events (TEAEs) were observed more commonly in participants in the eGFR <60 versus the ≥60 mL/min/1.73 m^2 subgroup. In the lower eGFR subgroup, TEAEs were reported in 64.7% and 59.4% of participants in the Gla-300 and Gla-100 treatment groups, respectively. In the higher eGFR subgroup, TEAEs were reported in 55.8% and 52.5% of participants in the Gla-300 and Gla-100 treatment groups, respectively. The proportion of participants who experienced at least one TEAE relating to injection site reaction, hypersensitivity, cardiovascular events, and acute kidney injury, are shown in Supplementary Table 6.

Participant satisfaction

There were no differences in patient satisfaction either by eGFR subgroup or treatment arms. The mean (SD) change in total DTSQ score from baseline to month

6 in the higher eGFR subgroup was 3.53 (6.50) and 3.93 (6.84) with Gla-300 and Gla-100, respectively. In the lower eGFR subgroup, mean change was 3.01 (6.43) and 3.30 (6.44) with Gla-300 and Gla-100, respectively. The LS mean difference (SE) between Gla-300 vs Gla-100 in total DTSQ scores after 6 months of treatment was −0.22 (0.21) in the higher eGFR subgroup, compared with −0.33 (0.46) in the lower eGFR subgroup.

Discussion

This patient-level meta-analysis from the EDITION 1, 2 and 3 trials of participants with T2DM by baseline eGFR subgroup demonstrated consistent and comparable reductions in FPG and HbA_{1c} levels for the Gla-300 and Gla-100 groups, regardless of renal function subgroup. This finding was accompanied by a lower risk of nocturnal confirmed (≤70 mg/dL [≤3.9 mmol/L]) or severe hypoglycemia with Gla-300 than Gla-100, which was not influenced by renal function. Hence, overall the pooled results presented here are consistent with the individual EDITION studies,[14-16] which also reported comparable glycemic control and reduced risk of hypoglycemia with Gla-300 compared with Gla-100. Importantly, however, these data show that this advantage of Gla-300 over Gla-100 was maintained in people with T2DM and impaired renal function. While the results of this patient-level meta-analysis are encouraging and suggest that Gla-300 therapy may also be used in people with T2DM and renal impairment, the scarcity of literature on insulin use in this population, and the post hoc nature of this analysis, highlight the need for

randomized clinical trials to more fully evaluate the impact of renal function and CKD on diabetes therapy.

As expected, participants with lower eGFR experienced higher incidence and rates of hypoglycemia. While the mean insulin doses increased in both treatment arms, there was a tendency for a larger increase with Gla-300, consistent with findings reported for the overall EDITION population.[14-16] Although speculative, one possible reason underlying this greater increase in dose with Gla-300 than Gla-100 may be related to the lower bioavailability of Gla-300, owing to the greater stability of its subcutaneous depot that might make it more prone to enzymatic inactivation compared with Gla-100.[18] It is also important to consider that the dose changes observed may be a consequence of the treat-to-target design of the EDITION trials; dose increases were to be expected given that participants switched to, or initiated, a new basal insulin in this study because they were uncontrolled on their previous treatment. In a meta-analysis of the EDITION studies, Gla-300 was associated with lower weight gain despite higher doses compared with Gla-100,[18] and the current analysis demonstrates a similar trend in participants with renal impairment.

Of note, the higher insulin doses observed in the EDITION studies with Gla-300 were not associated with an increased risk of hypoglycemic events, and the mean insulin doses were comparable between renal function subgroups in this analysis. Differences between renal function subgroups in the relative increases of insulin dose are unlikely to account for the higher incidence of hypoglycemia in the lower

eGFR subgroup as, if anything, dose increases were lower in the <60 mL/min/1.73 m^2 than the ≥60 mL/min/1.73 m^2 subgroup. Furthermore, the pooled data show that renal function did not change after treatment with either Gla-300 or Gla-100 for 6 months. These findings suggest that the observed differences between the renal subgroups in the rate and incidence of hypoglycemia were unlikely to be related to dose or dose increase, but are consistent with the higher risk for hypoglycemia reported in CKD.[11] In terms of safety, as expected, TEAE incidence was generally higher in the lower versus the higher eGFR subgroup, but there were no major differences in TEAEs between Gla-300 and Gla-100 within the two subgroups, nor between either renal function or treatment groups for injection site reactions, hypersensitivity, cardiovascular events or acute kidney injury.

The 2016 ADA guidelines do not include specific HbA_{1c} targets for individuals with T2DM and renal impairment, although goals that are less stringent than the general target of 7.0 % (e.g. <8.0 %) are suggested for people with comorbidities.[21] Indeed, the current analysis demonstrates that HbA_{1c} targets of <7.5 % are achievable for many people with T2DM. Furthermore, the reduced risk of hypoglycemia with Gla-300 is particularly important in this patient group, where there is a high risk of cardiovascular disease, as the experience of hypoglycemia may be associated with cardiovascular events and mortality.[22]

This post hoc analysis provides data supporting the use of Gla-300 in individuals with T2DM and mild renal impairment, which will help inform and guide management

decisions. The comparison with Gla-100 is important, as this is the gold standard of treatment in many countries. The lower risk of hypoglycemia with Gla-300 than Gla-100 is of particular interest as the risk of hypoglycemia is increased in people with renal impairment,[11] therefore therapy options with lower risk of hypoglycemia may be particularly beneficial in this population. Basal insulin therapy requires a balance between achieving appropriate individualized glycemic targets and minimizing or avoiding hypoglycemia. Consistent with the data here in participants with impaired renal function, a meta-analysis of EDITION 1, 2 and 3 data indicated that treatment with Gla-300 could allow people with T2DM to achieve equivalent glycemic control vs Gla-100 but with less hypoglycemia.[23]

The limitations of this analysis included its post hoc nature and the exclusion of participants with severe renal impairment (CKD stage 5) from the EDITION program. In addition, the lower number of participants with eGFR <60 mL/min/1.73 m^2 compared with the ≥60 mL/min/1.73 m^2 subgroup lead to wider confidence intervals for the hypoglycemia results for this subgroup compared with the ≥60 mL/min/1.73 m^2 subgroup, although the absolute point estimates were similar between each subgroup (Figures 2B and 3B). However, this analysis provided hypothesis-generating data that may be explored further by stratifying participants according to renal function in future randomized controlled clinical studies, dedicated to evaluating insulin treatment in participants with T2DM.

In summary, as previously demonstrated overall in the EDITION program, Gla-300 had comparable effectiveness as Gla-100 in improving glycemic control in a group of challenging to treat people with T2DM and renal impairment; this clinical goal was achieved in tandem with a consistent overall reduction in the risk of nocturnal confirmed (≤70 and <54 mg/dL [≤3.9 and <3.0 mmol/L]) or severe hypoglycemia, with no significant difference between renal function subgroups.

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Conflicts of interest disclosure

The authors report the following dualities of interest:

J.E. has participated in advisory panels for MSD, Novo Nordisk, and Sanofi, and has participated in speaker's bureau for AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD, Novo Nordisk, and Sanofi. S.H. has participated in advisory boards, conferences and acted as a consultant for Ascensia, AstraZeneca, Bayer, Becton-Dickinson, Boehringer Ingelheim, Janssen, Lifescan, Eli Lilly, MSD, Novartis, Novo Nordisk, and Sanofi. P.S. has participated in advisory panels, advisory boards, and

acted as a consultant for Abbott, AstraZeneca, Eli Lilly, Genzyme, GlaxoSmithKline, Janssen, Medtronic, Novo Nordisk, Sanofi, and Servier, received research support from AstraZeneca, Boehringer Ingelheim, Prometic, Novo Nordisk, Sanofi, Servier, and Viacyte, and participated in speaker's bureaus for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Lifescan, Novartis, Novo Nordisk, Sanofi, and Valeant. M.B. and A.C. are employees of Sanofi. L.M.-M is an employee of IVIDATA Group, providing consultancy to Sanofi. J.K. has received research support from AstraZeneca and Sanofi, and participated in speaker's bureaus for AstraZeneca, Boehringer Ingelheim, Eli Lilly, and Janssen. R.R. has acted as a consultant for AstraZeneca, MSD, Novo Nordisk, Sanofi, and Servier, and participated in speaker's bureaus for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, MSD, Novartis, Novo Nordisk, and Sanofi.

Author contributions

M.B. and A.C. were involved in the design of the meta-analysis and acquisition of the data. L.M.-M performed the statistical analysis of the data. All authors had access to the relevant study data and interpreted data, reviewed and commented on several drafts of the manuscript, and had final responsibility to submit the article for publication. J.E. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

[1] Tuttle KR, Bakris GL, Bilous RW*, et al.* Diabetic kidney disease: a report from an ADA Consensus Conference. Am J Kidney Dis. 2014; **64**: 510-533

[2] Saran R, Li Y, Robinson B*, et al.* US Renal Data System 2015 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis. 2016; **67**: A7-8

[3] New JP, Middleton RJ, Klebe B*, et al.* Assessing the prevalence, monitoring and management of chronic kidney disease in patients with diabetes compared with those without diabetes in general practice. Diabet Med. 2007; **24**: 364-369

[4] Szczech LA, Stewart RC, Su HL*, et al.* Primary care detection of chronic kidney disease in adults with type-2 diabetes: the ADD-CKD Study (awareness, detection and drug therapy in type 2 diabetes and chronic kidney disease). PLoS One. 2014; **9**: e110535

[5] Nitta K, Okada K, Yanai M, Takahashi S. Aging and chronic kidney disease. Kidney Blood Press Res. 2013; **38**: 109-120

[6] Alsahli M, Gerich JE. Hypoglycemia in Patients with Diabetes and Renal Disease. J Clin Med. 2015; **4**: 948-964

[7] Pathak RD, Schroeder EB, Seaquist ER*, et al.* Severe Hypoglycemia Requiring Medical Intervention in a Large Cohort of Adults With Diabetes Receiving Care in U.S. Integrated Health Care Delivery Systems: 2005-2011. Diabetes Care. 2016; **39**: 363-370

[8] National Kidney Foundation. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. Am J Kidney Dis. 2012; **60**: 850-886

[9] Inzucchi SE, Bergenstal RM, Buse JB*, et al.* Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015; **38**: 140-149

[10] Hyre AD, Fox CS, Astor BC, Cohen AJ, Muntner P. The impact of reclassifying moderate CKD as a coronary heart disease risk equivalent on the number of US adults recommended lipid-lowering treatment. Am J Kidney Dis. 2007; **49**: 37-45

[11] Moen MF, Zhan M, Hsu VD*, et al.* Frequency of hypoglycemia and its significance in chronic kidney disease. Clin J Am Soc Nephrol. 2009; **4**: 1121-1127

[12] Busch M, Nadal J, Schmid M*, et al.* Glycaemic control and antidiabetic therapy in patients with diabetes mellitus and chronic kidney disease - cross-sectional data from the German Chronic Kidney Disease (GCKD) cohort. BMC Nephrol. 2016; **17**: 59

[13] Becker RH, Dahmen R, Bergmann K, Lehmann A, Jax T, Heise T. New insulin glargine 300 Units . mL-1 provides a more even activity profile and prolonged glycemic control at steady state compared with insulin glargine 100 Units . mL-1. Diabetes Care. 2015; **38**: 637-643

[14] Riddle MC, Bolli GB, Ziemen M*, et al.* New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using basal and

mealtime insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 1). Diabetes Care. 2014; **37**: 2755-2762

[15] Yki-Jarvinen H, Bergenstal R, Ziemen M*, et al.* New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). Diabetes Care. 2014; **37**: 3235-3243

[16] Bolli GB, Riddle MC, Bergenstal RM*, et al.* New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naive people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). Diabetes Obes Metab. 2015; **17**: 386-394

[17] Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care. 2005; **28**: 1245-1249

[18] Ritzel R, Roussel R, Bolli GB*, et al.* Patient-level meta-analysis of the EDITION 1, 2 and 3 studies: glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus glargine 100 U/ml in people with type 2 diabetes. Diabetes Obes Metab. 2015; **17**: 859-867

[19] Cherney DZ, Perkins BA, Soleymanlou N*, et al.* Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation. 2014; **129**: 587-597

[20] Wanner C, Inzucchi SE, Zinman B. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med. 2016; **375**: 1801-1802

[21] Standards of Medical Care in Diabetes-2016: Summary of Revisions. Diabetes Care. 2016; **39 Suppl 1**: S4-5

[22] Zoungas S, Patel A, Chalmers J*, et al.* Severe hypoglycemia and risks of vascular events and death. N Engl J Med. 2010; **363**: 1410-1418

[23] Bonadonna RC, Yale J-F, Brulle-Wohlhueter C, Boëlle-Le Corfec E, Choudhary P, Bailey TS. Hypoglycemia as a Function of HbA_{1c} in Type 2 Diabetes (T2DM): Insulin Glargine 300 U/mL in a Patient-Level Meta-analysis of EDITION 1, 2, and 3. Diabetes. 2016; **65 (Supplement 1)**: A239

Figure Legends

Figure 1A. Mean change in HbA_{1c} from baseline to month 6 according to renal function subgroup (mITT population)

CI, confidence interval; LS, least squares; eGFR, estimated glomerular filtration rate; mITT, modified intent-to-treat; MMRM, mixed model for repeated measurements; †Logistic method; p<0.05 corresponds to significant heterogeneity of treatment effect

Figure 1B. Percentage of participants achieving HbA_{1c} targets (<7.0 % [53 mmol/mol] and <7.5 % [58.5 mmol/mol]) at month 6 (mITT population)

eGFR, estimated glomerular filtration rate; mITT, modified intent-to-treat;

Figure 2A. Percentage of participants experiencing ≥1 confirmed or severe hypoglycemic event (safety population)

eGFR, estimated glomerular filtration rate

Figure 2B. Relative risk of experiencing ≥1 hypoglycemic event with Gla-300 versus Gla-100 by renal function subgroup (safety population)

CI, confidence interval; eGFR, estimated glomerular filtration rate; †Logistic method; p<0.05 corresponds to significant heterogeneity of treatment effect

Figure 3A. Rate of confirmed or severe hypoglycemia by renal function subgroup (safety population)

eGFR, estimated glomerular filtration rate

Figure 3B. Ratio of annualized hypoglycemia event rates by renal function subgroup (safety population)

CI, confidence interval; eGFR, estimated glomerular filtration rate; †Logistic method; $p<0.05$ corresponds to significant heterogeneity of treatment effect

Table 1. Baseline demographics and participant characteristics, by renal function subgroup (pooled randomized population)

Renal function subgroups, baseline eGFR (mL/min/1.73 m^2)	<60		≥60	
	Gla-300 (N=208)	Gla-100 (N=213)	Gla-300 (N=1039)	Gla-100 (N=1036)
Mean age, years	65.0 (7.9)	65.0 (7.5)	57.4 (9.0)	57.2 (9.3)
Gender (male), n (%)	109 (52.4)	101 (47.4)	548 (52.7)	548 (52.9)
Race, n (%)				

Caucasian/White	188 (90.4)	199 (93.4)	908 (87.4)	896 (86.5)
Black	13 (6.3)	5 (2.3)	77 (7.4)	89 (8.6)
Asian/Oriental	4 (1.9)	7 (3.3)	44 (4.2)	42 (4.1)
Other	3 (1.4)	2 (0.9)	10 (1.0)	9 (0.9)
Body weight, kg	101.2 (21.3)	99.5 (20.5)	99.6 (23.2)	99.9 (22.0)
BMI, kg/m^2	35.5 (7.0)	35.4 (6.3)	34.5 (6.9)	34.7 (6.4)
Estimated GFR, mL/min/1.73 m^2	49.0 (8.5)	48.2 (9.6)	85.1 (16.6)	85.0 (16.6)
HbA_{1c}, %	8.2 (0.8)	8.1 (0.8)	8.3 (0.9)	8.4 (0.9)
HbA_{1c}, mmol/mol	66.3 (9.2)	65.2 (8.3)	67.5 (10.2)	67.9 (10.1)

Hemoglobin, g/L				
Males	138.4 (14.3)	140.3 (15.8)	146.0 (11.6)	145.6 (12.1)
Number of males below gender specific range, n (%)	19 (17.4)	17 (16.8)	22 (4.0)	26 (4.7)
Females	128.2 (13.4)	128.3 (12.32)	132.6 (11.3)	132.3 (12.0)
Number of females below gender specific range, n (%)	15 (15.2)	18 (16.1)	33 (6.7)	35 (7.2)
Albumin creatinine ratio assessed, n	201	210	1018	1013

Categories				
<30 mg/g, n (%)	120 (59.7)	136 (64.8)	777 (76.3)	784 (77.4)
30–300 mg/g, n (%)	54 (26.9)	50 (23.8)	204 (20.0)	198 (19.5)
>300 mg/g, n (%)	27 (13.4)	24 (13.4)	37 (3.6)	31 (3.1)
Duration of diabetes, years	15.7 (7.8)	15.9 (7.9)	12.1 (7.0)	12.0 (7.3)
Duration of basal insulin, years†	5.7 (4.9)	6.1 (4.5)	5.1 (4.4)	4.9 (4.3)
Basal daily insulin dose, U/kg†	0.67 (0.23)	0.69 (0.26)	0.67 (0.25)	0.67 (0.25)

Total daily insulin dose, U/kg‡	1.22 (0.54)	1.25 (0.45)	1.19 (0.48)	1.19 (0.45)
Previous antihyperglycemic medication excluding insulin, n (%)	154 (74.0)	161 (75.6)	912 (87.8)	919 (88.7)
Biguanides	134 (64.4)	145 (68.1)	876 (84.3)	877 (84.7)
Metformin	115 (55.3)	118 (55.4)	702 (67.6)	715 (69.0)
Metformin hydrochloride	17 (8.2)	28 (13.1)	173 (16.7)	164 (15.8)
Sulfonylureas	47 (22.6)	39 (18.3)	229 (22.0)	230 (22.2)
Dipeptidyl peptidase-4 (DPP-4) inhibitors	26 (12.5)	31 (14.6)	97 (9.3)	118 (11.4)

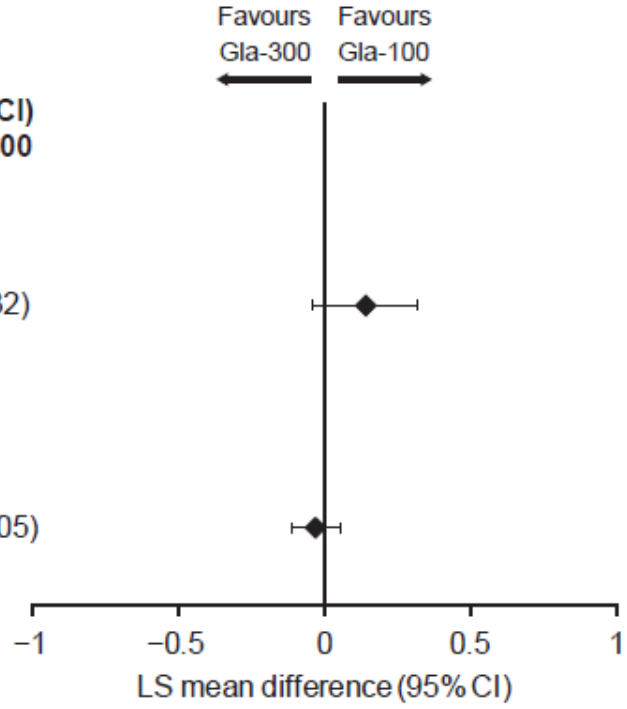
Previous insulins and analogs, n (%)	152 (73.1)	150 (70.4)	656 (63.1)	661 (63.8)
Insulin glargine	134 (64.4)	128 (60.1)	543 (52.3)	579 (55.9)
Insulin detemir	1 (0.5)	2 (0.9)	7 (0.7)	3 (0.3)
Insulin degludec	0 (0)	0 (0)	0 (0)	1 (<0.1)
Any statins, n (%)	149 (71.6)	150 (70.4)	570 (54.9)	591 (57.0)
Antihypertensive agents, n (%)	185 (88.9)	177 (83.1)	760 (73.1)	774 (74.7)
Any ACE inhibitors	108 (51.9)	107 (50.2)	463 (44.6)	477 (46.0)

Any other antihypertensive agents	24 (11.5)	26 (12.2)	66 (6.4)	74 (7.0)

Data are pooled from EDITION 1, 2 and 3, and are presented as mean (SD), unless otherwise indicated**.** †Only EDITION 1 and 2. ‡Only EDITION 1. ACE, angiotensin converting enzyme; BMI, body mass index; eGFR, estimated glomerular filtration rate (derived using the Modification of Diet in Renal Disease [MDRD] study equation)

Figure 1A. Mean change in HbA_{1c} from baseline to month 6 according to renal function subgroup (mITT population)

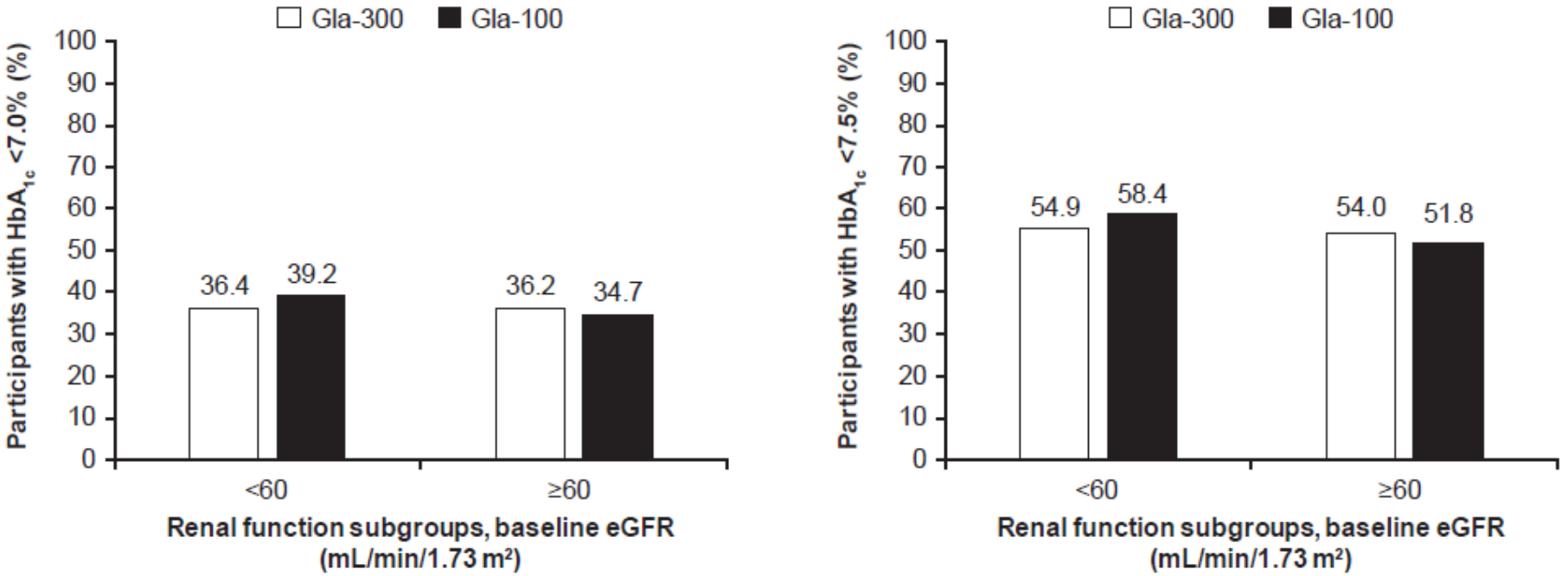
Renal function subgroup, baseline eGFR (mL/min/1.73 m²)	Treatment group	Mean HbA_{1c} at baseline (%)	Mean mean HbA_{1c} at month 6 (%)	LS mean change (SE)	LS mean difference (95% CI) Gla-300 vs Gla-100
<60	Gla-300 (n=206)	8.21	7.27	−0.98 (0.07)	0.14 (−0.04 to 0.32)
	Gla-100 (n=209)	8.10	7.10	−1.12 (0.06)	
≥60	Gla-300 (n=1033)	8.32	7.25	−1.03 (0.03)	−0.03 (−0.11 to 0.05)
	Gla-100 (n=1026)	8.36	7.30	−1.00 (0.03)	



Heterogeneity of treatment effect across subgroups: p=0.097†

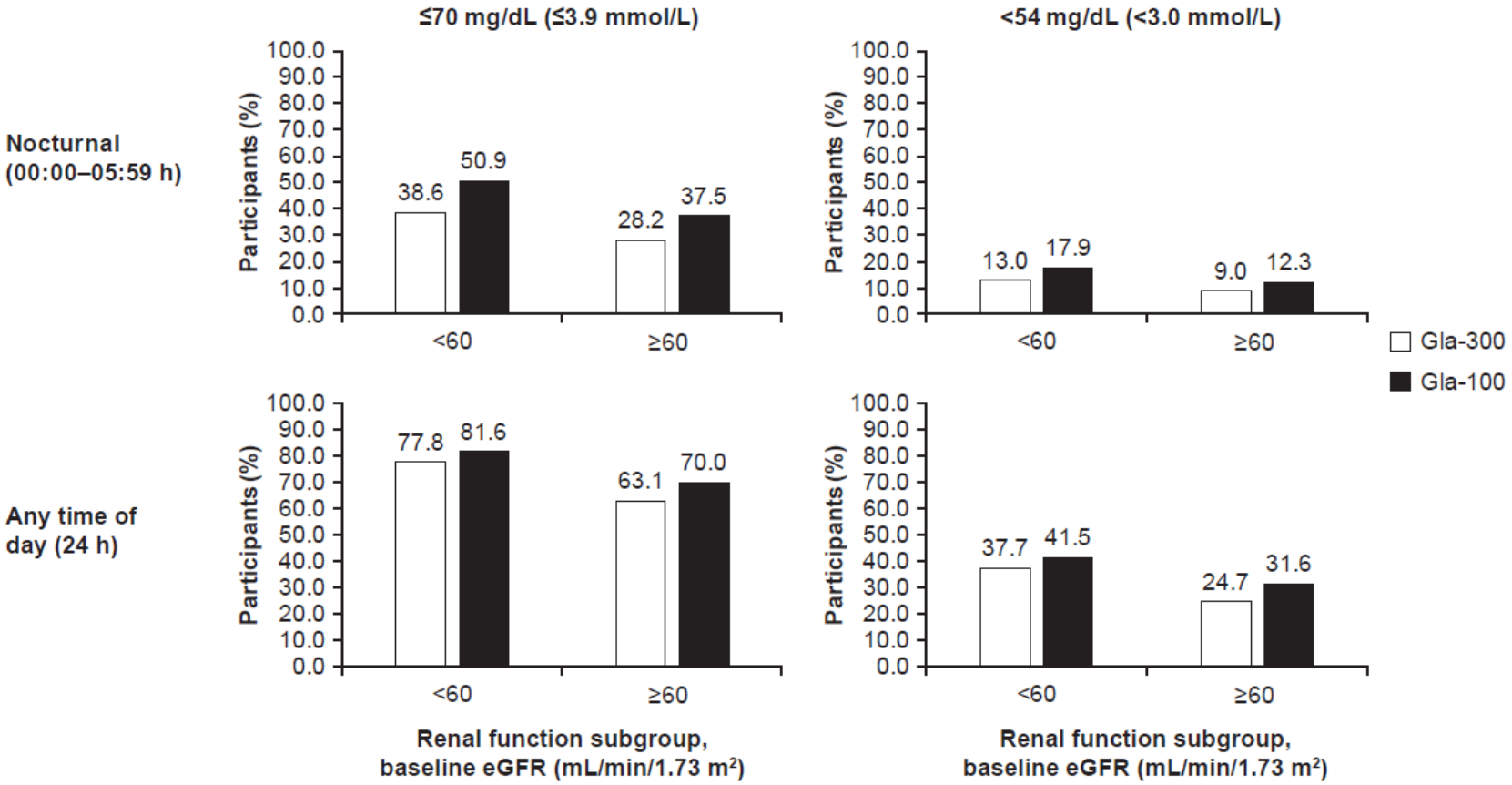
CI, confidence interval; LS, least squares; eGFR, estimated glomerular filtration rate; mITT, modified intent-to-treat; MMRM, mixed model for repeated measurements; †Logistic method; $p<0.05$ corresponds to significant heterogeneity of treatment effect

Figure 1B. Percentage of participants achieving HbA_{1c} targets (<7.0 % and <7.5 %) at month 6 (mITT population)



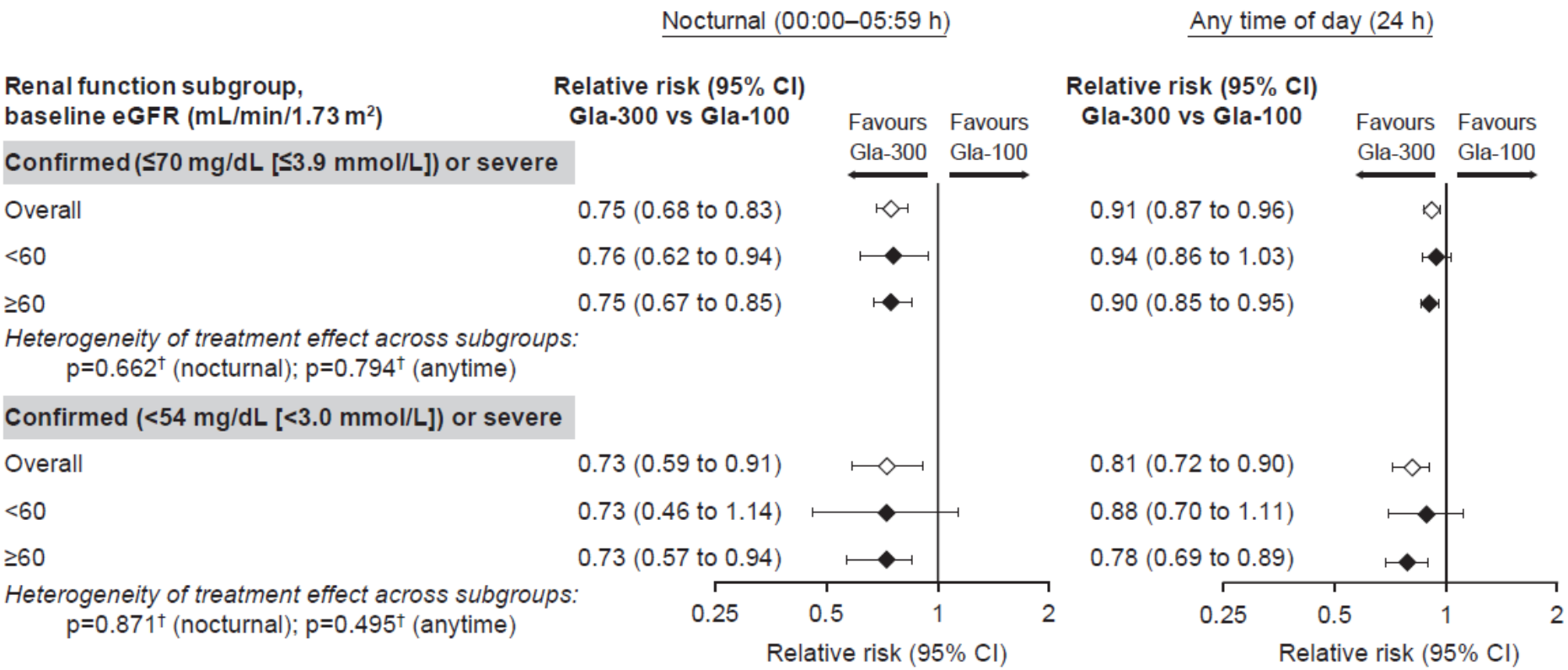
eGFR, estimated glomerular filtration rate; mITT, modified intent-to-treat

Figure 2A. Percentage of participants experiencing ≥1 confirmed or severe hypoglycemic event (safety population)



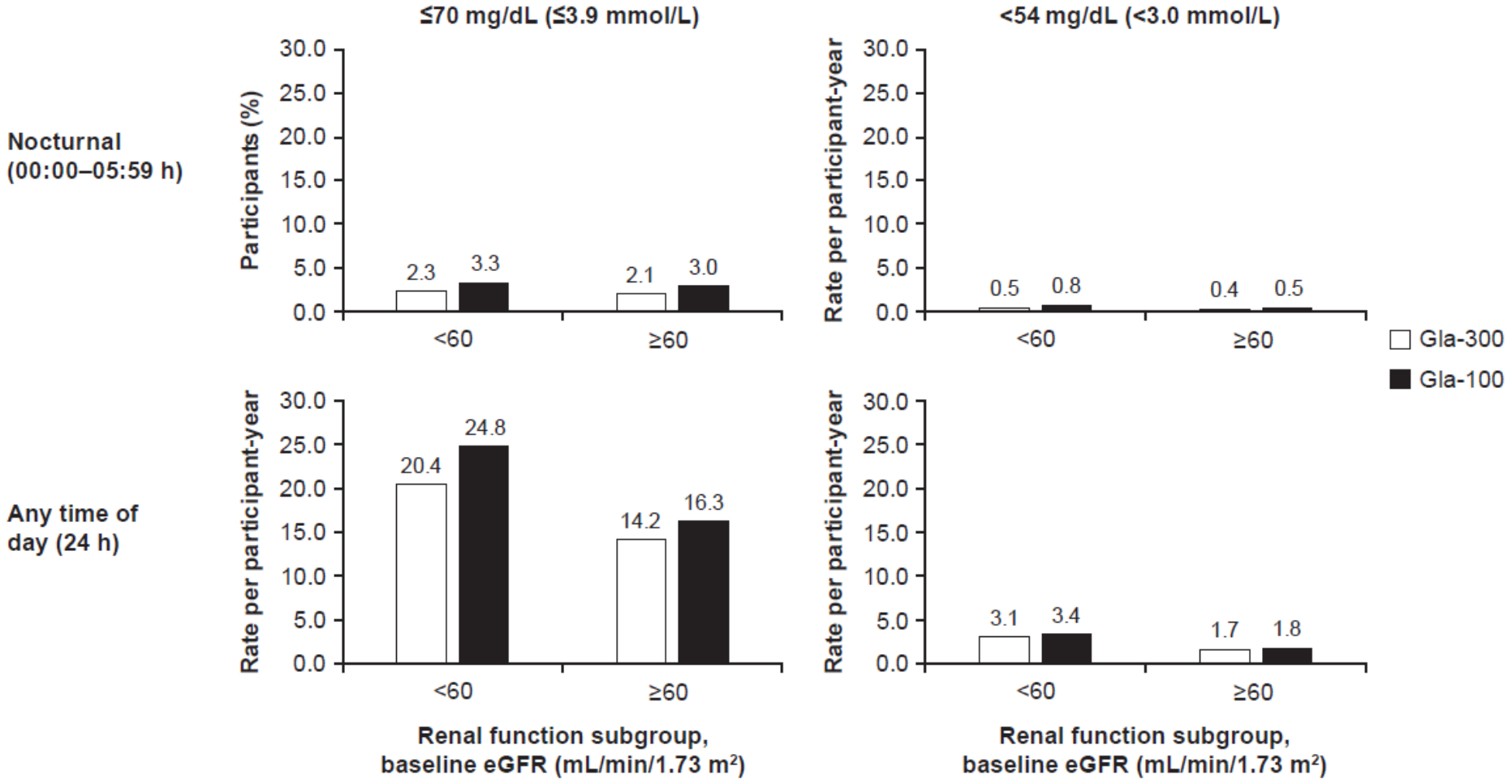
eGFR, estimated glomerular filtration rate

Figure 2B. Relative risk of experiencing ≥1 hypoglycemic event with Gla-300 versus Gla-100 by renal function subgroup (safety population)



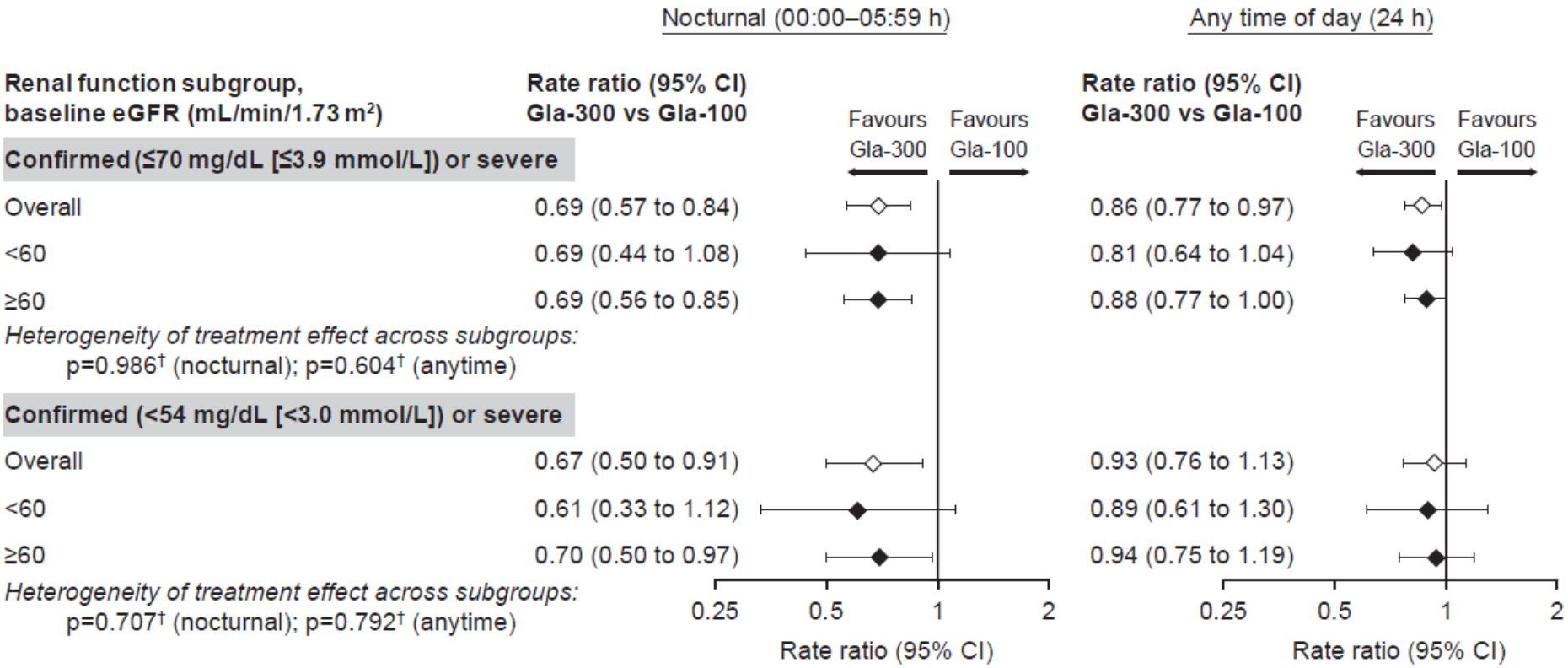
CI, confidence interval; eGFR, estimated glomerular filtration rate; †Logistic method; $p<0.05$ corresponds to significant heterogeneity of treatment effect

Figure 3A. Rate of confirmed or severe hypoglycemia by renal function subgroup (safety population)



eGFR, estimated glomerular filtration rate

Figure 3B. Ratio of annualized hypoglycemia event rates by renal function subgroup (safety population)



CI, confidence interval; eGFR, estimated glomerular filtration rate; †Logistic method; $p<0.05$ corresponds to significant heterogeneity of treatment effect